



Division of Tuberculosis
Prevention and
Control, Massachusetts
Department of Public Health

Medical Advisory Committee for the Elimination of Tuberculosis

Interim guidelines for use of an Interferon- γ Release Assay (IGRA) to diagnose tuberculosis infection

Recently a new generation of tests for patients with latent tuberculosis infection (LTBI) has become available to many Massachusetts practitioners. These tests, like the existing tuberculin skin test (TST), detect immune responses to the causative organism, *Mycobacterium tuberculosis* (Mtb). While employing technically different methods, resulting in different performance characteristics, both tests (Quantiferon-Gold-In-Tube and T-SPOT TB) measure the release of the cytokine interferon- γ from blood cells in response to stimulation by Mtb components. Thus, we refer to them collectively as interferon- γ release assays (IGRAs). As of this posting, the Quantiferon-Gold-In-Tube is commercially available in some locations in the U.S.; T-SPOT TB is under review by the FDA, with approval expected shortly.

IGRAs have several advantages over the traditional TST. Test cutoffs are objective and interpretation does not require specialized skills in the clinic. Patients do not have to return to have tests read, although those with positive tests still require follow up counseling. And, most importantly, IGRAs use components not found in the strain *Mycobacterium bovis* BCG, the vaccine used in much of the world. While TST can occasionally be misleadingly positive in vaccinated individuals, particularly those who received multiple vaccinations or who were immunized at older ages, IGRAs are highly specific for reactivity to *M. tuberculosis*. Repeated TSTs can also boost non-specific reactions due to BCG or non-tuberculous mycobacterial infections, whereas IGRAs are not subject to boosting. However, IGRAs also have drawbacks. They require phlebotomy and the blood must be transported to the lab in a timely fashion. They are also likely to be more expensive than TST, though expenses will vary considerably with personnel and transportation costs.

Because IGRAs are new, we have only limited information about their appropriate use. The absence of a gold standard test for LTBI makes their evaluation difficult. Most (but not all) existing studies compare IGRAs with TST rather than examining the test's ability to identify patients with LTBI. While the Centers for Disease Control and Prevention (CDC) and Canadian Tuberculosis Council have both issued recommendations, these are already being revised, and a group of experts we convened had considerable disagreement on the proper use of these tests. Thus, recommendations will likely change, as more data become available. While the optimal use of these tests is not yet clear, IGRAs are being widely used in parts of the US and Europe.

Here we present some consensus recommendations. These are not intended to be substitutes for a good history and clinical evaluation, or for expert consultation in difficult cases. While the currently available IGRA tests may or may not perform optimally in every situation, the TST is highly sensitive, but lacks specificity. The recommendations for use of the IGRA tests in specific situations are as follows:

- Recent contacts of tuberculosis cases. Some data suggest that IGRAs perform well in this population and can be used to identify newly infected patients.
- Recent immigrants. The panel was unable to reach a consensus on appropriate testing. While individuals with positive IGRA might represent a group at high risk of developing disease, a negative IGRA test may not rule out LTBI. The long-term clinical risk of persons with IGRA negative tests but positive TST reactions is unknown at this time.
- Occupational health screening. Either TST or IGRA might be appropriate. Again, for new employees, a negative IGRA result may not rule out LTBI, and the long-term clinical significance is not known.
- Immunocompromised individuals. These fall into two groups:
 - o For patients who are not immunocompromised but are about to initiate immunosuppressive therapy (e.g., chemotherapy, transplant or anti-TNF [anti-tumor necrosis factor] agents), it might be reasonable to use both TST and IGRA and to consider treatment for LTBI if either is positive. If clinical factors suggest high risk of LTBI, treatment should be considered despite negative IGRA and TST.
 - o For patients with a currently immunocompromising condition (e.g., HIV infection, hematologic malignancy and those on immunosuppressive therapy); because both TST and IGRA rely on an intact immune response, both have limited sensitivity in such patients. Therefore, it might be reasonable to use both tests and to consider treatment for LTBI if either is positive.
- Low risk individuals. All tests for LTBI are imperfect and, in a person with a low pretest probability of infection, results are very difficult to interpret. In principle, people with little risk of LTBI should not be evaluated using any of these tests because positive reactions are more likely due to non-specific reactions than LTBI. (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm>). However, testing of low-risk individuals is still required for some jobs. Under these circumstances, the lack of cross-reactivity of IGRAs to antigens present in BCG and most environmental mycobacteria may be advantageous.
- Children. There are currently few data available to make any recommendation for use of IGRAs in children
- Active tuberculosis. IGRAs, like the TST, are more likely to be positive in patients with active tuberculosis than in persons without tuberculosis. However, neither IGRAs nor TST should be relied upon to diagnose or rule out active TB disease.

(October 17, 2008)